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Marrow fibroblasts induce monocytes to promote endogenous regeneration

Circulating monocytes can transmigrate the vascular wall, enter a specific tissue, and differentiate into macrophages to perform functions relevant to that microenvironment (ME). Using the bone marrow as a model ME we focused on the ability of marrow fibroblasts to provide signals to monocytes. These marrow fibroblasts appear to remain constant in their support of continuous "regeneration", otherwise known as blood cell production. To study marrow fibroblasts we isolated and immortalized distinct fibroblast lines from normal human marrow: one designated HS27a expresses CD146, IGA3, and maintains early progenitors in culture. Monocytes co-cultured with HS27a assume a macrophage phenotype and express genes that function in tissue and organismal development. We also cloned a canine equivalent of HS27a, designated DS1, to be used *in vivo* in canine models of ischemia-induced myocardial infarction (MI) and radiation-induced pulmonary fibrosis (PF). 10^7 DS1 cells were infused intravenously after establishing the existence of an injury: 2 weeks post-infarction in the MI model and 5 weeks after irradiation in the PF model. In both, recovery of function was significantly improved in dogs given DS1 cells compared to controls. Histological examination of tissue at necropsy also showed significant differences between DS1 treated dogs and controls. The more complete tissue regeneration was observed in the lung model in which dogs were euthanized 21 weeks after treatment, whereas MI dogs were euthanized only 2 weeks after treatment. Importantly 48 hours after infusion there was no evidence by PCR of DS1 cells in the regenerating tissues or in the blood. This was in agreement with previous studies using ^{111}In-DS1 cells which showed the DS1 cells are trapped in the lung where they are destroyed. However within 6 hours of DS1 infusion circulating monocytes expressed activation markers, and between 2 and7 days post DS1 infusion, large colonies of endothelial-like cells were grown from blood mononuclear cells. We propose that circulating monocytes come in contact with and receive signals from the DS1 cells sequestered in the lung. These signals prepare the monocytes for recruitment to sites of injury where they scavenge debris and promote and regulate a multi-step process of endogenous regeneration.

Biography

Beverly Torok Storb is a full member of the Faculty at the Fred Hutchinson Cancer Research Center and Director of the Core Center of Excellence in Hematology. Her research focuses on dissecting the marrow microenvironment to understand the regulation of blood cell production and endogenous regeneration.

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